UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/158,120	09/21/1998	LESLIE SID JOHNSON	469201-367	3563

7590 01/13/2003

RAYMOND LILLIE
CARELLA BYRNE BAIN GILFILLAN
CECCHI STEWART & OLSTEIN
6 BECKER FARM ROAD
ROSELAND, NJ 07068

EXAMINER	
ROARK, JESSICA H	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/13/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/158,120	JOHNSON, LESLIE SID	
	Examin r	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2002 and 21 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,10,13,21 and 22* is/are pending in the application.

4a) Of the above claim(s) *10,13 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/21/02 is acknowledged. The specification has been amended to provide SEQ ID NOS.

2. Claim status:
Claims 5, 8-9, 11-12 and 14-20 have been canceled previously.
Claims 1-4, 6-7, 10, 13 and 21-22 *are pending.*

3. Given the previous restriction requirement (12/20/99, Paper No. 4), which is hereby reiterated; claims 10, 13 and 22 stand withdrawn from consideration by the Examiner under 37 CFR 1.142(b), as being drawn to a nonelected invention; the requirement having been traversed Paper No. 5.

Claims 1-4, 6-7 and 21 *are under consideration in the instant application.*

4. The formal drawings submitted 9/9/02 have been approved by the Draftsman.

5. Applicant's previous amendment of the specification to contain specific reference to the earlier filed application is again acknowledged. However, the status of nonprovisional parent applications (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

6. The abstract of the invention is not descriptive. A new abstract *not to exceed 150* words is required that is clearly indicative of the invention *to which the claims are directed.*

7. This Office Action will be in response to applicant's arguments, filed 9/9/02 (Paper No. 19).
The rejections of record can be found in the previous Office Action (Paper No. 17).

8. The previous objection to the specification is objected to as failing to provide proper antecedent basis for the claimed limitation of comprises a framework region, "at least a portion of which" is human is withdrawn.

9. The previous rejection of claims 2-4, 6-7 and 21 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicant's comments filed 9/9/02.

10. The previous rejection of claims 2-4, 6-7 and 21 under 35 U.S.C. 112, first paragraph, *New Matter,* is withdrawn.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1-4 and 21 stand rejected under 35 U.S.C. 102(a) as being clearly anticipated by Tempest et al. (Biotechnology, March 1991, vol 9, pages 266-271, of record) for the reasons of record originally set forth in Paper No. 9, mailed 4/26/00.

Applicant's arguments, filed 9/9/02 have been full considered but have not been found sufficient.

Applicant argues that the Johnson Declaration filed on 10/30/00 under 37 CFR 1.131, in combination with the Exhibits furnished on 9/9/02, is sufficient to overcome the Tempest et al. (Biotechnology, March 1991, vol 9, pages 266-271, of record) reference.

The Johnson Declaration filed on 10/30/00 under 37 CFR 1.131, in combination with the Exhibits furnished on 9/9/02, has been considered but is ineffective to overcome the Tempest et al. reference.

It is unclear from the Declaration as filed that the contributions of Ms. Lisa Bennett and Mr. David Pfarr were made under the direction of Dr. Johnson.

In addition, the Johnson 1.131 Declaration does not clearly set forth that there was conception, diligence and reduction to practice with respect to all limitations taught by Tempest et al. and recited in the instant claims. Although it is noted that the evidence provided in Exhibits 2-4 do involve a neutralizing anti-RSV F antigen antibody, Applicant is invited to clarify the Declaration with respect to the claimed limitations.

Given the absence of additional rebuttal to the outstanding rejections of record in Applicant's Response filed 9/9/02 (Paper No. 19); the rejection is maintained for the reasons of record in Paper Nos. 9 and 13.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-4, 6-7 and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tempest et al. (Biotechnology, March 1991, vol 9, pages 266-271, of record) in view of Beeler et al. (J. Virol. 1989; 63:2941-2950, of record) for the reasons of record set forth originally in Paper No. 9, mailed 4/26/00.

Applicant's arguments, filed 9/9/02 have been full considered but have not been found sufficient.

Applicant argues that the Johnson Declaration filed on 10/30/00 under 37 CFR 1.131, in combination with the Exhibits furnished on 9/9/02, is sufficient to overcome the Tempest et al. (Biotechnology, March 1991, vol 9, pages 266-271, of record) reference.

The Johnson Declaration filed on 10/30/00 under 37 CFR 1.131, in combination with the Exhibits furnished on 9/9/02, has been considered but is ineffective to overcome the Tempest et al. reference.

It is unclear from the Declaration as filed that the contributions of Ms. Lisa Bennett and Mr. David Pfarr were made under the direction of Dr. Johnson.

In addition, the Johnson 1.131 Declaration does not clearly set forth that there was conception, diligence and reduction to practice with respect to all limitations taught by Tempest et al. and recited in the instant claims. Although it is noted that the evidence provided in Exhibits 2-4 do involve a neutralizing anti-RSV F antigen antibody, Applicant is invited to clarify the Declaration with respect to the claimed limitations.

Given the absence of additional rebuttal to the outstanding rejections of record in Applicant's Response filed 9/9/02 (Paper No. 19); the rejection is maintained for the reasons of record in Paper Nos. 9 and 13.

15. Claims 1-4, 6-7, and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al. (Nature, 1986; 321:522-525, of record) in view of Beeler et al. (J. Virol. 1989; 63:2941-2950, of record) for the reasons of record set forth originally in Paper No. 9, mailed 4/26/00.

Applicant's arguments, filed 9/9/02 have been full considered but have not been found sufficient for the reasons of record.

The rejection of record may be found in Paper No. 9.

Applicant argues in the response filed 9/9/02 that Beeler et al. teach only murine antibodies and do not teach or suggest which, if any, of the murine monoclonal anti-RSV antibodies could be humanized.

Applicant also argues that Jones et al. teach only the replacement of the heavy chain CDRs of an antibody which does not bind RSV. Applicant further argues that Jones does not teach the therapeutic application of CDR substitution into a human antibody.

However, as previously noted in Paper No. 9, Jones et al. on pages 524-525 do teach the applicability of "humanization" of antibodies, including replacement of all CDRs, for therapy in humans.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA).

Further, it is noted that the instant independent claims are generic and do not require an anti-RSV antibody of any particular specificity. Neither do any of the instant claims recite a particular antibody from which the CDRs are derived.

The rejection is maintained for the reasons of record in Paper No. 9.

16. Claims 1-4, 6-7 and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Queen et al. (U.S. Pat. No. 5,693,762, of record) in view of Beeler et al. (J. Virol. 1989; 63:2941-2950, of record).

The claims are drawn to an antibody against respiratory syncytial virus (RSV) that comprises at least one complementarity determining region (CDR) of a murine monoclonal antibody against RSV; or that comprises a human constant region, framework regions at least a portion of which are human, and three (or possibly six, given the ambiguous wording) CDRs of murine origin, in particular from a neutralizing murine antibody against site A or site C of the RSV F protein.

Applicant's arguments, filed 9/9/02, have been fully considered but have not been found convincing for the reasons of record in Paper No. 17.

Applicant argues that Queen et al. do not teach or suggest a human-murine antibody against RSV, and that Beeler et al. teach only a murine anti-RSV antibody and do not teach which, if any anti-RSV antibodies should be humanized. Applicant concludes that the combination of the references therefore do not render obvious the instant claims.

It is believed that the rejection of record in Paper No. 17, reiterated below, addresses Applicant's arguments in full.

As previously noted, Queen et al. teach a method of producing high affinity "humanized" immunoglobulins (antibodies) in which one or more CDR, and possibly additional amino acids from the framework region, are replaced by donor immunoglobulin sequences (see entire document, e.g., as summarized in the Abstract). Queen et al. provide detailed guidance as to how to select "acceptor" human immunoglobulin sequences and make the appropriate replacement of CDRs, and if necessary, certain residues in the framework regions, to produced a humanized antibody that retains the high affinity for antigen of the donor antibody (see entire document, especially the Summary of the Invention at columns 2-3). Queen et al. also teach that "humanization" of rodent antibodies, including mouse antibodies, is important to reduce their immunogenicity in humans, making them better therapeutic reagents (see entire document, e.g., columns 1-3 or column 16).

Queen also teaches humanization of anti-viral mouse antibodies (see especially columns 26-29 and 32-35). Queen teaches that it is important to humanize anti-viral antibodies in order to provide non-immunogenic, efficacious antibodies for therapy of human viral infections (see especially column 32 at line 66 thru column 33).

Queen et al. do not teach humanization of murine antibodies to RSV in general, or humanization of neutralizing antibodies against the A or C site RSV F protein in particular.

Beeler et al. have been discussed previously and teach the production of neutralizing murine monoclonal antibodies to the RSV F protein, including antibodies to antigenic site A and antigenic site C of the F protein (see entire document). Beeler et al. review the art recognized clinical importance of RSV as one of the most important causes of respiratory tract illness in children worldwide and the role of antibodies in providing protection against RSV infection (e.g., page 2941, first paragraph). Beeler et al. also teach that the immune response to the F protein is important for neutralization of heterologous viral strains, and that antigenic sites A and C are relatively stable (see especially introduction on page 2941 and Discussion on page 2948, first full paragraph).

Given the teachings of the references, it would have been obvious to the ordinary artisan at the time the invention was made to apply the humanization methodology taught by Queen et al. to the neutralizing murine antibodies to the RSV F protein taught by Beeler et al. One of ordinary skill in the art would have had a reasonable expectation of successfully producing antibodies against RSV that comprised at least one and preferably three CDRs from each of the heavy chain and light chain variable regions of the murine anti-RSV F protein site A or C antibodies taught by Beeler et al. given the detailed methodology for replacing CDRs and producing high affinity antibodies taught by Queen et al. Antibodies humanized according to the teachings of Queen et al. would have also comprised a human constant region and a heavy and light chain variable region that itself comprised a framework region at least a portion of which was human.

Both Queen et al. and Beeler et al. teach antibody neutralization of viruses, and Queen et al. teach that humanized antibodies are more effective and efficacious antibodies for therapy of humans. Thus the ordinary artisan at the time the invention was made would clearly have been motivated to modify the RSV neutralizing antibodies of Beeler et al. to provide therapeutic reagents against a clinically important virus. In particular, the ordinary artisan would have been motivated to select anti-RSV antibodies which bound antigenic sites A or C of the RSV F protein for modification according to the method of Queen et al. because Beeler et al. teach that these sites are antigenically stable among RSV virus types, and so antibodies to these sites would have offered the broadest applicability as therapeutic agents for neutralization of RSV.

Given the teachings of antibodies having specificity for sites A and C of the RSV F protein, methods for introducing at least one and preferably three CDRs from the heavy and light chain variable regions of these antibodies into human antibody sequences, methods for transferring other murine framework residues as needed to result in high affinity humanized antibodies (a framework at least a portion of which is human), and a clear motivation for making these changes to the mouse antibodies so that they could more effectively be used a therapeutic agents; the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. It is again acknowledged that Applicant filed a Terminal Disclaimer on 10/30/00 (Paper No. 12) disclaiming the terminal portion of any patent granted on the instant application which is subsequent to the expiration date of U.S. Patent No. 5,824,307.

18. No claim is allowed.

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
January 13, 2003

Phillip Gambel
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
1/13/03